27. (New) The kit of claim 25 comprising an antigenic part of the protein consisting of the amino acid sequence of Accession number Y08612, for use as a control sample.

28. (New) The kit of claim 26 comprising an antigenic part of the protein consisting of the amino acid sequence of Accession number Y08612, for use as a control sample.

REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons which follow.

I. STATUS OF THE CLAIMS

Claims 1-11 have been cancelled, without prejudice or disclaimer thereof, claim 12 remains unamended, and claims 13-28 have been added to the application. Applicants reserve the right to prosecute the subject matter of the cancelled claims in this or another application.

Because the amendments to the claims do not introduce new matter, as discussed more fully below, entry thereof by the Examiner is respectfully requested.

II. SUMMARY OF THE INVENTION

The invention is directed to a method for diagnosing the existence of carcinomas, sarcomas, or a combination thereof, in a mammal by determining the level of expression of the protein bearing Accession number Y08612, referred to as "Nup88," in a tissue biopsy sample. The level of expression can be assessed by determining the quantity of an antibody that binds to Nup88. Alternatively, the level of expression can be assessed by determining the level of

annealing of a nucleic acid, such as a DNA or RNA probe, to a nucleic acid encoding Nup88.

III. THE OFFICE ACTION

A. Rejection of the Claims Under 35 U.S.C. §112, First Paragraph

Claims 1-11 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Office Action at page 2. Applicants respectfully traverse this ground for rejection.

1. The Examiner's Basis For Rejection of the Claims

In support of this ground for rejection, the Examiner stated that one of skill in the art would need to "perform extensive and undue experimentation" to practice the claimed method with a reasonable expectation of success. To elaborate, the Examiner stated at page 3 of the Office Action that there is:

(1) "no working exemplification of the claimed method for diagnosing the existence of any and all types of malignant carcinoma and sarcoma in any and all mammals";

(2) "no working exemplification of the claimed method for diagnosing the pathological developmental stage of [or the grade of] any and all types of malignant carcinoma and sarcoma in any and all mammals"; and

(3) "no factual evidence of record that the invention can be used effectively in a clinical setting" (Office Action at page 3).

The Examiner concluded by stating that "one skilled in the art would not accept the assertion that the invention can be used effectively to diagnose the presence, stage, or grade of any carcinoma or sarcoma in any mammal." Office

Action at page 3.

Furthermore, in summing up the results of Tockman et al., *Cancer Research, 52*:2711s-2718s (1992), at page 5 of the Office Action, the Examiner surmised that "clearly, prior to the successful application of newly described markers, validation against acknowledged disease end-points must occur and the markers' predictive value must be confirmed in prospective population trials."

2. Applicants' Claimed Invention Meets the Statutory Standard for Enablement

a. Contrary to the Examiner's Assertion, Working Examples Exemplify the Use of the Claimed Invention in Diagnosing A Variety of Tumors in a Variety of Tissue Types

Applicants respectfully disagree with the Examiner's assertion that there is "no working exemplification of the claimed method for diagnosing the existence of any and all types of malignant carcinoma and sarcoma." Applicants provide extensive guidance and teachings throughout the specification on how to diagnose the existence of a carcinoma or a sarcoma, or both, from a variety of different tissues, by determining the level of expression of Nup88. Indeed, Applicants conclude, at page 20, lines 27-29 of the specification, that "our findings suggest that this molecule [*i.e.*, "Nup88"] may be a potentially significant marker **given its dramatic overexpression in a broad spectrum of malignant tumors** of literally all denominations."

Moreover, Table 1 at pages 21-23 lists **more than fifty** cancers, in addition to mesenchymal and miscellaneous tumors, that applicants tested for the overexpression of Nup88 in almost a dozen different organs. One of skill in the art knows that "overexpression" is a relative term that refers to levels of expression of a particular protein between a control, *i.e.*, "normal" sample, and a test sample, *i.e.*, an abnormal, or diseased sample.

In particular, the examples given in the specification teach:

(1) almost a dozen organs that are amenable to the screening method of the claimed invention;

(2) over fifty cancers that can be screened for overexpression of Nup88; and

(3) detailed and referenced methodologies for conducting the screening of biopsy samples to determine the level of expression of Nup88 as well as for quantifying the level of expression of Nup88 in those biopsy samples.

Applicants teach the level of antibody binding to Nup88 protein in cells of tissues selected from the (1) stomach, (2) colon, (3) liver, (4) pancreas, (5) breast, (6) lung, (7) uterus, (8) prostate, (9) kidney, (10) adrenal, and (11) mesenchymal tissues. *See* Table 1 of the specification. Applicants also describe the extent of antibody binding to Nup88 in tissue samples obtained from these organs at page 12, line 8, to page 16, line 23, of the application.

Applicants tested for the overexpression of Nup88 in the tissue biopsies from organs clinically diagnosed with, for example, *infiltrating adenocarcinoma, in situ carcinoma, villous adenoma, tubular adenoma, neuroendocrine carcinoma, hepatocellular carcinoma, dysplastic nodules, infiltrating ductal carcinoma, infiltrating lobular carcinoma, fibroadenomas, fibrocystic disease, squamous carcinoma, broncholoalveolar carcinoma, large cell carcinoma, carcinoid, hyperplastic bronchi, cystadenoma, borderline serous carcinoma, borderline mucinous carcinoma, endometrial carcinoma, endometrial hyperplasia, benign glandular hyperplasia, cortical adenoma, fibrosarcoma, Kaposi sarcoma, angiolipoma, lymphoblastic lymphoma, Hodgkin's disease, glioblastoma multiforme, and dermatofibrosarcoma protruberous*. In fact, applicants tested "a total of **266 samples**, including 230 surgical tissues, 20 adult autopsy samples, and 16 fetal autopsy samples," to determine whether overexpression of Nup88

correlates with cancerous tissue types. *See* page 10, line 31, through page 11, line 1, of the application.

Applicants teach at page 10, line 24, through to page 12, line 5, **exactly** how to test for overexpression of Nup88 in biopsy samples: "All tissues had been fixed in formalin ... sections for immunostaining were cut at 4 µm, deparaffinized in xylene ... immunostaining was accomplished by the avidin-biotin-peroxidase method ... best results were obtained when the antiserum was applied overnight in a humid chamber at 4°C ..." *See* page 11 of the application. Furthermore, Applicants teach how to conduct immunoblot analysis using the "ECL" system (Amersham, U.K.) for densitometric quantification of antibody binding to Nup88. *See* pages 11 and 16 of the application.

The Examiner is respectfully requested to note that the claimed invention does not recite the testing of the inventive method in "any and all mammals." Rather, Applicants seek to apply the inventive method to identify a cancerous tissue sample, that ultimately is from a mammal, preferably a human.

Thus, it is clear that there is no undue experimentation imposed upon a skilled artisan attempting to practice the claimed invention. MPEP § 2164.01 states that the standard test for enablement is whether "the experimentation needed to practice the invention is undue or unreasonable. Given the guidance and teachings disclosed in the claimed application, the quantity of experimentation which would be required to practice the invention, if any, is not unwarranted or excessive. The skilled artisan, after reading the specification would know that one may use an antibody that binds to Nup88 to determine the level of expression of that protein in a cell. Furthermore, having read the specification, the skilled artisan would be apprised of the fact that if the level of expression of Nup88 in a test sample is at least between 1.5 and 5 times greater than that of a normal control sample, then that test sample contains cancerous cells.

b. Applicants Are Not Required to Test Every Possible Tumor Typ and Tissue Type to Enable the Claimed Invention under § 112, First Paragraph

The Examiner's implication that the specification is lacking experimental data to support the claimed invention is unwarranted because the law does not require a patent applicant to exemplify **every** species in a genus to show enablement of that genus. *See Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991). Rather, a specification must provide sufficient guidance to allow practice of the invention without undue experimentation. The specification need only describe procedures that can be practiced, without undue experimentation, to determine which embodiments are encompassed by the claims. See *e.g., In re Wands*, 858 F.2d 731 ("Practitioners of this [monoclonal antibody] art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.").

According to statute and well-accepted legal decisions and precedent, Applicants most definitely provide guidance for practicing the invention without undue experimentation such that the skilled artisan can determine which embodiments are encompassed by the claims.

c. The References Cited by the Examiner do not Rebut Applicants' Experimental Results

As a matter of PTO practice, an Applicants' disclosure is to be taken as *prima facie* enabling unless the PTO can present a scientific explanation calling into doubt, based on concrete reasons, the truth of that presumably enabling disclosure. No such reasoning has been set forth in the Office Action. The Examiner only has illuminated the state of the art with respect to the diagnosis of cancer as described in the work of various other groups. The examiner has not presented a scientific explanation why the claimed invention is allegedly not enabled.

More specifically, the work by other groups states that a single marker indicating the presence of cancer has not yet been found, and may be difficult to identify. Such prior art references only support the unexpected and surprising nature of Applicants' discovery.

Accordingly, there is no extensive and undue experimentation required of the skilled artisan for practice of the claimed invention. For at least the foregoing reasons, Applicants respectfully request withdrawal of this ground for rejection.

3. The Claimed Invention, As Amended, Does Not Recite Methods of Diagnosing the Grade or Stage of Different Cancers

The Examiner also rejected claims 1-11 as allegedly failing to be enabled for diagnosing the grade or stage of a cancer. While Applicants' respecfully disagree with this ground for rejection, claims 1-11 have been cancelled and claims 13-28 have been added to the application. The new claims do not recite a method for diagnosing the "pathological developmental stage" or the "grade" of "any and all types of malignant carcinoma and sarcoma in any and all mammals." Applicants reserve the right to prosecute the cancelled subject matter in this or another application. This amendment has been made for the sole purpose of advancing the prosecution of this case.

The Examiner's rejection is moot and, therefore, applicants kindly request withdrawal of this ground for rejection.

4. The Standard for Enablement Does Not Require a Showing of Usefulness in a Clinical Setting

In describing the prior art, the Examiner stated at page 5 of the Office Action that "prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end-points, establish quantitative criteria for marker presence/absence and confirm marker

predictive value in prospective population trials." Office Action at page 5. According to the Examiner, Applicants did not provide such data and, therefore, there is "no actual evidence of record that the invention can be used effectively in a clinical setting."

In contrast to the Examiner's assertion, Applicants used biopsies from individuals that had "acknowledged disease end-points." *See* page 10, line 24 of the application, where applicants state that "[C]ases were selected on the basis of **known diagnoses** ..." (emphasis added). Thus, Applicants "validate[d] the markers against acknowledged disease end-points." Moreover, as described above, Applicants also clearly "established quantitative criteria for marker presence/absence."

Furthermore, while the Examiner has extensively documented the need for population trials to establish the usefulness of a claimed invention in a clinical setting, this level of experimentation is not required for patentability. Merely because Applicants have not tested human subjects in a clinical setting does not mean that the present claims are not enabled.

MPEP § 2107.03 states that the Office must confine its review of patent applications to the statutory requirements of the patent laws. Other agencies are assigned the responsibility of ensuring conformance to standards established by statute for advertisement, use, sale or distribution or drugs. The FDA pursues a two-prong test: safety and efficacy. Thus, **FDA approval, and FDA requirements for establishing approval of a drug, are not prerequisites to enablement or patentability of an invention under 35 U.S.C 112, first paragraph**.

Also, according to MPEP § 2164.02, there is no requirement that *in vivo* testing be performed. MPEP § 2107.03 states that *in vitro* testing is generally sufficient to support therapeutic utility. The MPEP further states "[s]ince the initial burden is on the examiner to give reasons for the lack of enablement, the

examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. The Examiner has not shown that the *in vitro* results disclosed by Applicants in the claimed application do not correlate with cancerous tissues.

Given the above rationale, one skilled in the art would not be forced to perform extensive and undue experimentation to practice the claimed method as alleged by the examiner. Applicants therefore respectfully request that the examiner withdraw this rejection.

B. The Rejection of Claims 6, 8, and 12 for Failing to Meet Deposit Requirements

1. The Examiner's Basis For Rejection

Claims 6, 8, and 12 were rejected "because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited." *See* page 6 of the Office Action.

The Examiner also stated at page 7 that if a deposit has been made under the provisions of the Budapest Treaty, the submission of a declaration stating that the deposit has been accepted by an International Depository Authority and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would overcome the rejection. *See* page 8 of the Action.

2. Applicants' Declar All R strictions on the Deposit Will Be Irr vocably Removed Upon Grant of the Present Application

Filed herewith is a declaration, executed by Applicants' attorney of record, listing the depository, Accession number, and date at which the monoclonal antibody disclosed in the application was deposited at an International Depository Authority. The declarant also avows that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent for the claimed invention.

Applicants' declaration obviates the Examiner's rejection and, therefore, withdrawal of this ground for rejection is respectfully requested.

C. Rejection of Claims 1-11 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-11 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter of the present invention. Office Action at page 6.

Applicants canceled claims 1-11. Applicants' new claims, 13-28, do not recite the terms and phrases that the Examiner alleged were indefinite in claims 1-11.

The terms "and/or," "characterized by," "characterized in that," "Nup88," "homology," "virtually," "corresponding counterpart," are not recited in new claims 13-28. Claim 15, dependent from the method of claim 13, defines the positive step of determining the level of expression of the protein consisting of the amino acid sequence of accession number Y08612 as comprising "**binding** a protein binding molecule to said protein," *i.e.*, to Nup88. The nature of the protein binding molecule is disclosed at page 5, lines 7-9, of the specification. "Such protein binding molecules may be natural antibodies..."

Similarly, claim 16 requires the positive step of "**annealing** ... a nucleic acid binding molecule to a nucleic acid transcript encoding said protein," *i.e.*, encoding the Nup88 protein. A nucleic acid binding molecule may be, for example, a nucleic acid probe.

As Applicants' claims are definite, withdrawal of this ground for rejection is respectfully requested.

IV. CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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